Remarks

The withdrawal of the Restriction Requirement is gratefully acknowledged. Claims 10, 15 and 17 -26 are pending. Claims 15, 18, 24 and 25 have been cancelled without prejudice to pursuit in a continuation or divisional. Claims 15, 17, 19 and 26 are presently amended.

Currently amended Claims 15, 17, 19 and 26 stand rejected under 35 USC 112, first paragraph because it is alleged that the specification does not provide enablement for the treatment of "all disorders or diseases associated with orexin system dysfunctions". Applicants respectfully submit that the specification is enabling for the claims presented. The specification reports IC_{50} values for OX1 and OX2 receptor antagonist activity on a nanomolar level (page 33, lines 5 to 7). In addition, Wistar rat home cage telemetry data is reported (pages 35-36) which is indicative of effects upon sleep/activity levels of the subjects. One skilled in the art, armed with the data and total content of the disclosure would be enabled in the practice of the claims, especially in light of other informing content in the art.

The Examiner is encouraged to consider the voluminous published literature on the effects of orexin on sleep in various organisms. See for example:

Sakurai T. The neural circuit of orexin (hypocretin): maintaining sleep and wakefulness. Nature Reviews. Neuroscience, Vol 8; March 2007.

Sutcliffe J.G. & De Lecea L. The hypocretins: setting the arousal threshold. Nat Rev Neurosci 3, 339-49; 2002.

The literature provides a background for the enablement analysis since one of ordinary skill in the art would be expected to be conversant with the state of the art in their area of expertise. In short, one skilled in the art, when informed of the state of knowledge in the art relating to orexin would have adequate basis to predict success in treatment of the

claimed range of disorders when given the data presented in the specification. In addition, the Examiner is encouraged to review materials on preclinical and clinical trials of Almorexant or ACT-078573 (the common name and code name of the compound of the invention) for the treatment of primary insomnia (sample enclosed, more available at the company's website www.actelion.com).

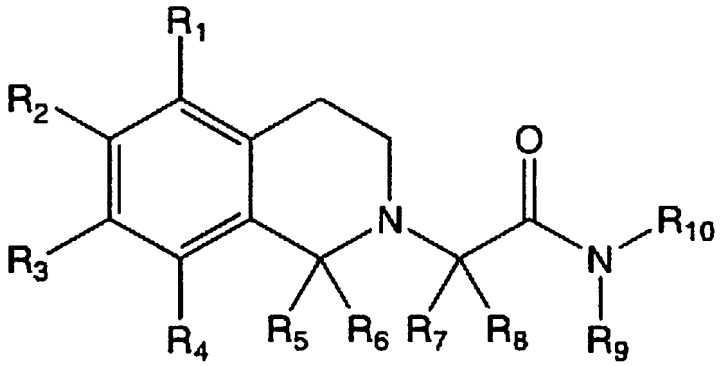
Applicants respectfully submit that the rejection of Claim 24 under 35 USC 112 is moot in light of the cancellation of Claim 24.

Claims 10, 15, 17, 19-23 and 26 are rejected under 35 USC 103(a) as being unpatentable over Actelion Pharmaceuticals LTD (Reference BA (WO 01/68609A) cited by Applicants. In support of this rejection the Examiner asserted that:

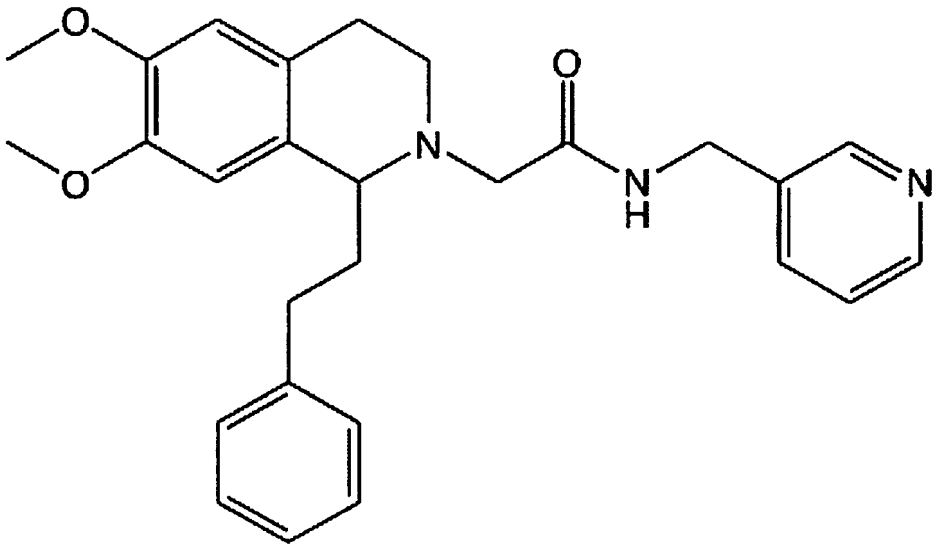
> "The instantly claimed invention is disclosed. At page 67, see example 110, the compound is disclosed as follows:
>
> 2-[1-(2-Phenyl-ethyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-3-yl-methyl)-acetamide:
>
> The difference between the prior art compound and the instantly claimed compound is R^7 or R^8. For the instantly claimed compounds, R^7 or R^8 represents phenyl. Howevcr, the cited compound in Reference BA teaches the R^7 or R^8 radical represents pyridinyl.
>
> It would have been obvious to one of ordinary skill in the art to replace the heterocyclyl in the pharmaceutical compound of Reference BA with another radical such as phenyl in view of the teaching of equivalence and the expectation of similar pharmaceutical properties. The compounds are deemed obvious variants. Accordingly, the claims are unpatentable therefrom."

Applicants respectfully point out that the structure of the compound of example 110 differs from the description set forth in the Office Action. The R^7 and R^8 positions on the indicated compound do not contain pyridinyl as asserted, but rather both are

hydrogen. In contrast to the description provided, the pyridin-3-yl-methyl group actually appears at either R^9 or R^{10} in the general formula.



Formula (I) of WO 01/068609



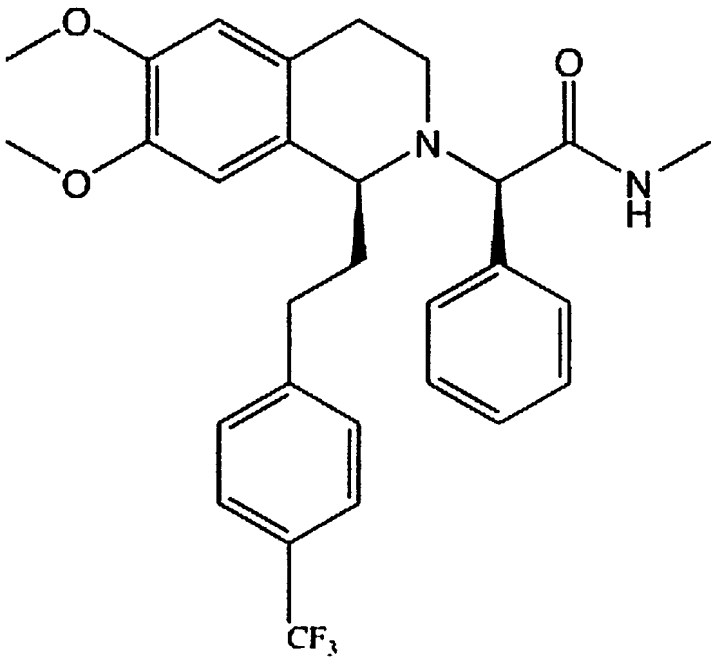
Compound 110 of WO 01/068609
2-[1-(2-Phenyl-ethyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-3-yl-methyl)-acetamide

Applicants respectfully submit that the compound of the invention is non-obvious over indicated compound 110 and over the disclosure of WO 01/068609 as a whole,

which describes a genus exemplified by 341 different specifically named compounds. Applicant's respectfully submit that the Examiner's argument does not conform with the recent Federal Circuit cases, requiring the identification of a lead compound and the rationale for the change away from the lead compound in the prior art. In particular, the Federal Circuit stated in *Eisai Co. v. Dr. Reddy's Lab.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008) that "post-KSR, a prima facie case of obviousness for a chemical compound still, in general begins with the reasoned identification of a lead compound". Similarly in *Takeda Chem. Industries, Ltd. V. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007), the Federal Circuit specifically states that "[i]n addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of 'adequate support in the prior art' for the change in structure" *Id.* at 1356. The Court went on to clarify: "[a] known compound may suggest its homolog, analog, or isomer because such compounds 'often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties.' [(citation omitted).] We clarified, however, that in order to find a prima facie case of unpatentability in such instances, a showing that the 'prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required.'." *Id.* (citations omitted).

Here the Examiner does not provide any showing of 'adequate support in the prior art' for several posited changes to an inaccurately described lead compound. Viewing the disclosure of WO 01/068609 as a whole, once skilled in the art would find that it describes a genus exemplified by 341 different specifically named compounds which differ from the compounds of the invention in at least three structural aspects. Of the 341 exemplified compounds, only three (compounds 110, 111 and 112) carry a phenyl-ethyl group in the corresponding position, however all of those phenyl-ethyl groups are unsubstituted. In contrast, the phenyl-ethyl group of the invention is substituted with trifluoromethyl at the 4-position and the disclosure provides no motivation to adopt this specific structural difference. In addition, none of compounds 110, 111 and 112 carry a second substituent at the 2-position of the acetamide, whereas the compound of the

invention carries a phenyl group at that position. Although compounds 4 and 5 have a phenyl group at the 2-position of the acetamide, they both have a 3,4-dimethoxy-benzyl group in place of the trifluoromethyl-phenyl-ethyl group in the compound of the invention. The disclosure provides no motivation to one skilled in the art to move from these structures toward the claimed invention. Additionally, none of the exemplified compounds of WO 01/068609 has a methyl group at position R9 or R10 in the general formula and the disclosure would provide no motivation to one skilled in the art to move from the disclosed structures to a structure containing a methyl group at position R9 or R10.



Compound of the Claims
(2R)-2-{(1S)-6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-*N*-methyl-2-phenyl-acetamide

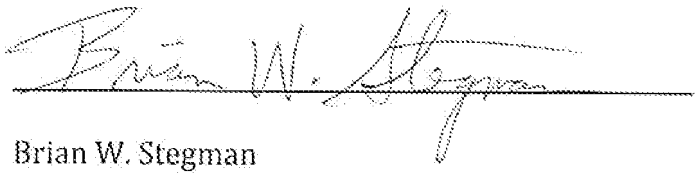
Finally, the compound of the claim, (2R)-2-{(1S)-6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-*N*-methyl-2-phenyl-acetamide, has a required specific absolute configuration which is neither taught nor suggested by WO 01/068609.

For the foregoing reasons, Applicants respectfully submit that the compound of the claim has been demonstrated to be non-obvious over the art. Accordingly, withdrawal of the rejections of record and allowance is respectfully requested.

Since this response is being filed within the shortened three-month statutory period set in the office action mailed on September 8, 2009, it is believed that no fees are due. If fees are deemed to be due, however, the Commissioner is authorized to charge any fees, or credit any overpayment, to Deposit Account No. 50-4255.

Respectfully submitted,

Date: December 8, 2009



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